



Commentary

TNF and HIV-1 Nef: An Intimate Interplay



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Chronic immune activation is a hallmark of HIV infection (Moir et al. 2011). Tumor necrosis factor (TNF) alpha is a proinflammatory cytokine detected throughout the disease course in plasma and lymph nodes of HIV-infected patients. The HIV-1 Nef protein is produced early during the disease and is present in several biological forms: a virion-associated protein, a free soluble plasma protein, and in plasma extracellular vesicles (pEV). A close interplay exists between Nef and TNF. Nef can mimic TNF action at the cellular level by activating similar pathways, including the NF- κ B, AP1, JNK and AKT pathways (Herbein and Khan, 2008; Kumar et al., 2016). Therefore, both TNF and Nef proteins favor immune activation, enhance HIV-1 transcription and replication, and fuel the progression of the disease. Although antiretroviral therapy (ART) efficiently suppresses HIV replication, immune activation and low CD4⁺ T cell counts often persist parallel to the presence of TNF and Nef in plasma.

The study by Ostalecki and colleagues in this issue of *EBioMedicine* describes an alternative TNF secretion mechanism where Nef-mediated routing of the TNF-converting enzyme ADAM17 into Rab4⁺ early endosomes and the Rab27⁺ secretory pathway leads to intracellular pro-TNF cleavage and secretion of vesicular TNF endosomes (Ostalecki et al. 2016—in this issue). Additionally, Notch1 is required for the endosomal trafficking of ADAM17. Besides a plasma membrane (PM)-associated TNF shedding, the study highlights that a larger pool of pro-TNF is cleaved intracellularly and secreted through vesicular endosomes. This alternative mechanism of TNF secretion was corroborated by careful analysis of lymph node sections from an aviremic patient under ART. Since both peripheral blood lymphocytes (PBLs) and monocytes produce TNF, it is critical to show that both cell types secrete TNF through vesicular TNF endosomes. This was indeed clearly demonstrated by incubation of both cell types with HIV-pEV, showing a typical secretion phenotype. In addition, endosomal TNF secretion from CD4⁺/CD45⁺ T cells was observed in a lymph node obtained from a non-viremic HIV-infected individual. The specific role of Nef in the secretion of vesicular TNF endosomes was further demonstrated since only vesicles generated from Nef-transfected HEK293T cells, but not from cells ex-

pressing other viral constructs known as TNF inducers, such as Tat, Vpr or Vpu, induced TNF secretion in target cells.

The presence of viral components has been reported in exosomes released from cells infected with Epstein-Barr virus, cytomegalovirus, herpes simplex virus and hepatitis C virus (Schorey and Harding, 2016). In HIV infection, Nef-expressing exosomes from infected cells favor viral replication (Arenaccio et al., 2014). The respective role of classical PM-associated TNF shedding and alternative endosomal TNF secretion in HIV pathogenesis has to be clarified in future studies. Although the authors report a preferential use of the alternative TNF pathway in the tissue sample studied, we cannot exclude the preferential activation of one pathway over the other depending on the stage of the HIV disease and/or the tissue studied.

Both Nef and TNF activate NF- κ B which enhances HIV-1 transcription and replication. So far, most studies have used soluble recombinant Nef and TNF proteins to assess their effects on the viral cycle. It would be of interest to decipher the effect of HIV-pEV on viral transcription and replication in several cell types including primary PBLs and monocytes/macrophages. In addition, Nef and TNF have been reported to favor the survival of productively infected CD4⁺ T lymphocytes, which requires endogenous Nef expression as well as activation by PM-associated TNF expressed on the surface of macrophages (Mahlknecht et al., 2000). The role of PM-associated TNF and vesicular TNF in Nef-mediated blockade of CD4⁺ T cell apoptosis has to be assessed in future studies. In fact, CD4⁺ T cell apoptosis has been reported to be increased following exposure to Nef-containing exosomes released from transfected T cell lines and could explain depletion of uninfected CD4⁺ T cells in HIV-infected patients (Lenassi et al., 2010). These apparently contradictory results could also depend on the type of cell releasing the vesicles, the target cells, and the viral and cellular components of the exosomes. Since the resistance to apoptosis of infected CD4⁺ T cells might participate in the formation and maintenance of viral reservoirs in HIV-infected people, the role of PM-associated TNF and vesicular TNF has to be studied in regard to HIV-1 latency. The persistent immune activation observed in non-viremic patients under ART especially in the presence of TNF and Nef could favor the formation of a viral reservoir (Siliciano and Siliciano, 2016). HIV integration and the establishment of latency in CCL19-treated resting CD4⁺ T cells have been shown to require activation of NF- κ B (Saleh et al., 2016). Since both TNF and Nef activate NF- κ B, the chronic immune activation observed in non-viremic patients

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under ART could impair the clearance of the viral reservoirs. New therapeutic approaches will need to control virus replication through ART but also to curtail immune activation with new therapeutic tools, possibly including anti-TNF agents.

Disclosures

The author declares no conflicts of interest.

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